PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, 31/44

A1

(11) International Publication Number: **WO 97/48380**

(43) International Publication Date: 24 December 1997 (24.12.97)

(21) International Application Number: PCT/SE97/01098

(22) International Filing Date: 18 June 1997 (18.06.97)

(30) Priority Data:
9602442-7 20 June 1996 (20.06.96) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CEDERBERG, Christer [SE/SE]; Åkergatan 1, S-431 69 Mölndal (SE). SACHS, George [US/US]; 17986 Boris Drive, Encino, CA 91316 (US).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ADMINISTRATION REGIMEN OF H^+, K^+-ATPase INHIBITORS

(57) Abstract

A new administration regimen giving an extended plasma concentration profile of a H^+, K^+-ATPase inhibitor. The extended plasma profile is received by two or more consecutive administrations of a unit dose of a H^+, K^+-ATPase with 0.5-4 hours interval or by a pharmaceutical composition with extended release, which may be administered once daily.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

ADMINISTRATION REGIMEN OF H^+, K^+-ATPase INHIBITORS

Field of the invention

The present invention is related to a new administration regimen of proton pump inhibitors, i.e. H^+, K^+-ATPase inhibitors. The new administration regimen gives an extended blood plasma concentration profile of the pharmaceutical substance, i.e. the proton pump inhibitors, thereby giving an improved inhibition of gastric acid secretion and an improved therapeutic effect. More specifically, the invention refers to the use of pharmaceutical preparations with a controlled release in the treatment of gastric acid-related diseases. The pharmaceutical preparation is preferably in the form of a dosage form which provides an extended and constant release of the acid labile H^+, K^+-ATPase inhibitor in the small and/or large intestines (but not in stomach) or a dosage form which provides two or more discrete pulses of release of the H^+,K^+-ATPase inhibitor in the small and/or large intestines (but not in stomach) separated in time with 0.5 - 4 hours. Furthermore, the present invention refers to the manufacture of such preparations.

Background of the invention

Acid labile H^+, K^+-ATPase inhibitors also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole. Some of these compounds are for instance disclosed in EP-A1-0005129, WO 94/27988, EP-A1-174726, EP-A1-166287 and GB 2163747.

These pharmaceutical substances are useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, they may be used for prevention and treatment of

gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrom. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, and in patients with symptomatic gastro-esophageal reflux disease. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these.

Therapeutic control of gastric acid secretion is fundamental in all theses discases, but the degree and duration of acid inhibition required for optimal clinical effect is not fully understood.

The duration of acid inhibition of one proton pump inhibitor such as for instance omeprazole is 3 - 4 days despite a plasma half-life of only 0.5 - 1 hour (Lind et al, Gut 1983;24:270-276)*)*. This lack of temporal relationship between plasma concentration of omeprazole and the degree of acid inhibition is due to the long-lasting binding of the active inhibitor to the gastric pump.

Proton pump inhibitors, such as the above discussed omeprazole, are generally administered as a single daily dose of 20 mg to 40 mg, depending on the gastrointestinal disorder as well as the severity of the disease. In the treatment of Zollinger-Ellison syndrom higher dosages of 60 - 120 mg/daily and as much as 360 mg/daily have been used. Generally, the proton pump inhibitor is adminstered to the patient during 2 - 4 weeks, in some cases up to 8 weeks. Omeprazole has also been used as maintainace therapy for peptic ulcer disease and reflux oesophagitis during many years.

Despite this long duration of acid inhibition once daily dosing results in not more than

70-80 % inhibition of maximal acid output prior to next dose. Results from *Helicobacter pylori* eradication studies have shown an improved efficacy with twice daily dosing in combination with antimicrobials. Treatment of severe GORD is also improved by divided doses as compared to single daily dose increments. These improved clinical effects are due to longer periods of high acid inhibition.

Although action of proton pump inhibitors is covalent, efficacy depends on active pumps and there are two pools of pumps, active and inactive. Only active pumps are covalently inhibited. The inactive pumps are recruited throughout the day therefore effectiveness of acid inhibition improves for 72 hours on once a day treatment, steady state being achieved as a balance between inhibition of active pumps and *de novo* biosynthesis or reversal of inhibition.

Extended release formulations to give blood plasma levels extending from 6-12 hours (by any of several means) will result in a larger fraction of the pumps being inhibited and should result in more effective inhibition of acid secretion resulting in improved efficacy in GORD, more rapid healing of gastric ulcer and improved eradication of *H. Pylori*.

Detailed description of the drawings

Figure 1 shows two graphs. These show the differencies between once daily administration and administration of two consecutive doses within 3 hours.

Summary of the invention

On a once a day administration regimen the maximal effect of omeprazole is about 75 % to 80 %, 24 hours after dose (Lind et al 1986, Scand J Gastroenterol (Suppl 118): 137 - 8 and Lind et al 1988, Scand J Gastroenterol 23: 1259 - 66), i.e. about 20 % to 25 % of the maximal gastric acid secretory capacity is present 24 hours after the dose. Even if an increased dose quantity of the proton pump inhibitor has been used (See Lind et al) the maximal gastric acid inhibition is limited to about 80 %.

The known dose dependency of gastric acid inhibition has hithereto resulted in a recommendation to initially increase the dose of the proton pump inhibitor, if a low response on the therapy or lack of response is obtained.

It has now been proposed according to the present invention to extend the plasma concentration profile of proton pump inhibitors and thereby improving their therapeutic effect. According to one aspect of the invention the extended plasma profile is provided by once daily administration of a dosage form which releases the proton pump inhibitor with an almost constant rate during an extended time period. According to another aspect of the invention the extended plasma profile is provided by once daily administration of a dosage form which, in the small and/or large intestines (but not in the stomach), releases the proton pump inhibitor in discrete pulses separated in time by 0.5 - 4 hours. It is also possible to obtain an extended plasma profile of a proton pump inhibitor by consecutive administrations of two or more unit doses with 0.5 - 4 hours intervals.

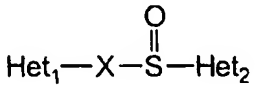
Detailed description of the invention

Acid secretion by the gastric mucosa is a property of the parietal cell. Whereas the functional regulation of this cell is a complicated process involving several different cell types with different receptors, acid transport *per se* is the property of a single P-type ATPase, the gastric H^+, K^+-ATPase. Therefore, effective therapeutic control of acid secretion involves either receptor blockade or gastric H^+, K^+-ATPase inhibition. This invention relates to the proton pump inhibitors and their reaction with the gastric acid pump. The half-life in plasma of the proton pump inhibitors is rather short. The administered proton pump inhibitor reacts with the active gastric acid pumps available for inhibition during that time. Un-inhibited, inactive pumps will be present during this time and pumps will recover following biosynthesis and reversal of inhibition. Therefore, by a repeated regimen or a dosage form which provides an extended plasma profile of the proton pump inhibitors recovered pumps as well as un-inhibited pumps not previously

available will react with the newly administered dose or pulse of pharmaceutical substance or the continuously released substance.

By administration of a pharmaceutical dosage form with an extended release, the plasma concentration of the pharmaceutical substance can be kept on a high level during an extended time. As a result the number of pumps inhibited by the proton pump inhibitor will increase and a more efficient therapeutic control of acid secretion will be obtained.

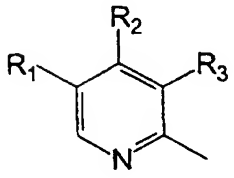
Compounds of interest for the novel administration with a repeated dosing regimen as well as for the controlled release preparations/compositions giving an extended plasma profile according to the present invention are compounds of the general formula I



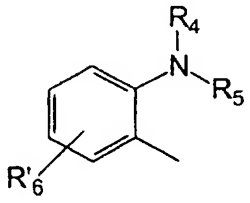
I

wherein

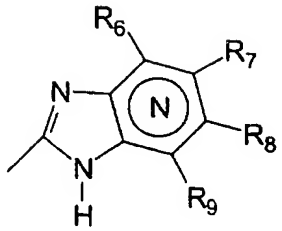
Het_1 is



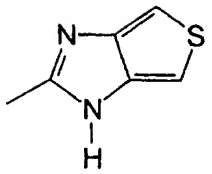
or



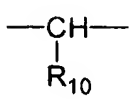
Het_2 is



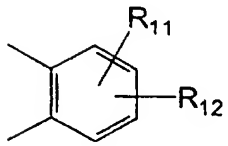
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

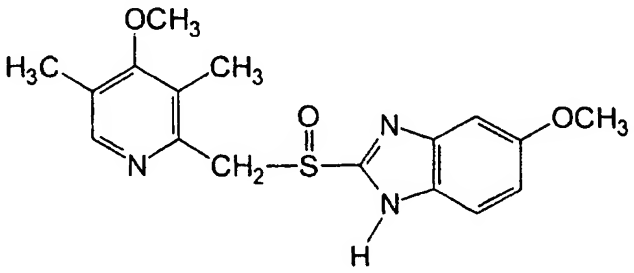
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

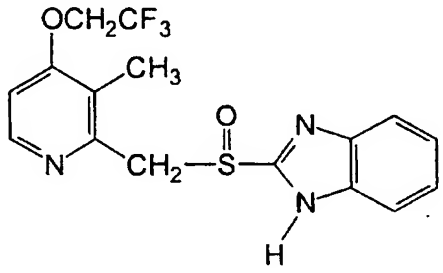
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

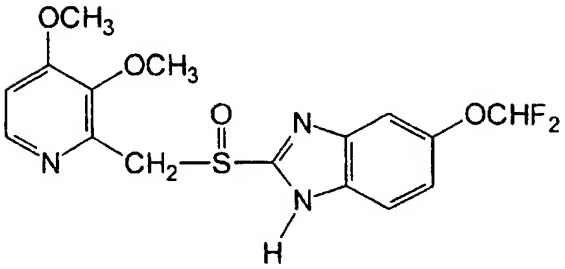
R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

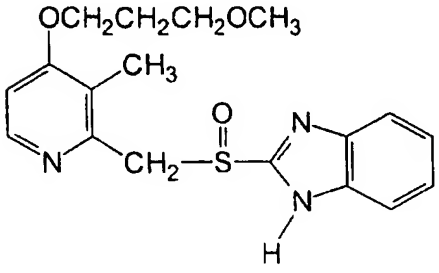
Examples of specifically interesting compounds according to formula I are

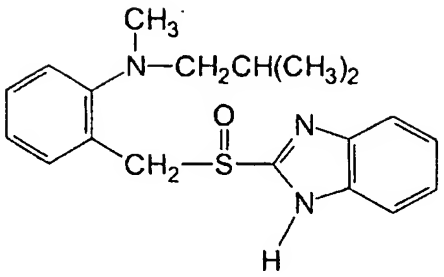


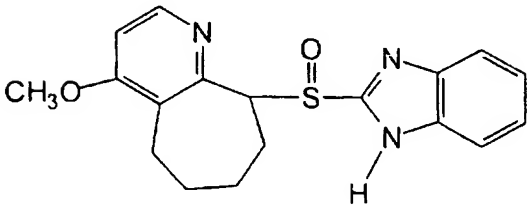
(Ia)

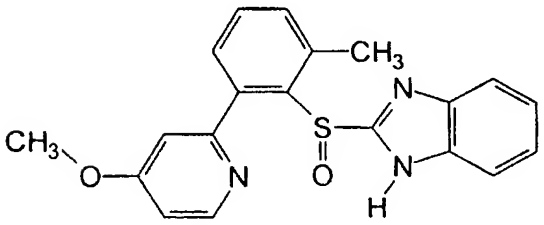


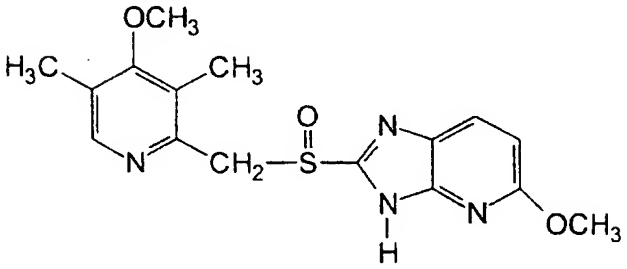


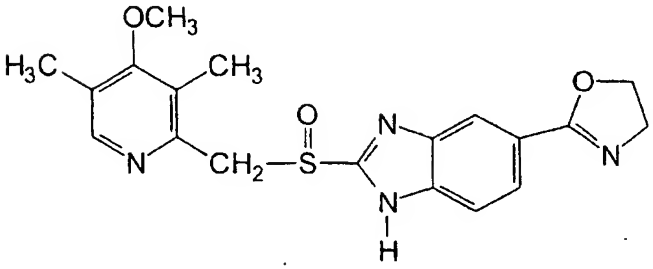


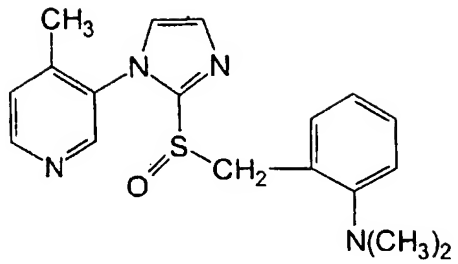












The compound used in the administration regimen as well as in the controlled release preparations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

Preferred compounds for the administration regimen and the oral pharmaceutical preparation according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. Thus, the substances being acid labile proton pump inhibitors are best protected from contact with acidic gastric juice by an enteric coating. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230. An enteric coated tablet of omeprazole magnesium salt is described in WO 95/ 01783. A tableted multiple unit dosage form of omeprazole is described in WO 96/ 01623. Pharmaceutical preparations manufactured according to known principles as described in the specifications US-A 4,853,230, WO 95/ 01783 and WO 96/ 01623, hereby incorporated in whole by references, may be used for administration with an increased dosing frequency according to the present invention.

A unit dosage of the proton pump inhibitor, for instance 1 - 500 mg is administered at least twice a day. The unit dosage may be given with a dosing frequency of about 0.5 - 4 hours, preferably two doses are given during a time period of 2 to 3 hours. Suitable doses comprise for instance 5, 10, 15, 20, 30 and 40 mg of the pharmaceutical substance.

In another embodiment of the invention an extended plasma profile is obtained by administration of a unit dose of a proton pump inhibitor which releases the drug for absorption in the small and/or large intestines in discrete pulses seperated in time by 0.5 - 4 hours.

Alternatively, an oral pharmaceutical formulation with extended release of the pharmaceutical substance during 2 - 12 hours, preferably 4 - 8 hours may be administered. Such an extended release preparation may comprise up to 500 mg of the substance, preferably the doses comprise about 5 - 100 mg of the substance, and more preferably 10 - 80 mg.

Different techniques for manufacturing of various controlled release preparations are for example described in Aulton M.E. (Churchill Livingstone Ed.), Pharmaceutics: The science of dosage form design (1988), p. 316-321.

The invention is described more in detail by the following examples.

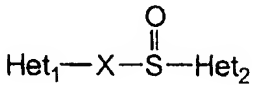
Examples

Omeprazole (Prilosec® capsules) 40 mg once daily (adminstered at 8.00 a.m.) or 20 mg given twice daily (adminstered at 8.00 a.m. and at 11.00 a.m.) given during five consecutive days were compared regarding effect on peptone stimulated gastric acid secretion and intragastric acidity measured on days 1 to 3 and day 5 in eigth healthy subjects. During the first two days of treatment there was a significantly ($p>0.05$) lower number of hours with high acidity (pH>1) when omeprazole was given twice daily, 20 mg administered with 3 hours apart, compared to a single morning dose of 40 mg. There was

also a significantly higher degree of hihibition of peptone stimulated acid output 24 hours post dose during the first three days of treatment. See Figure 1. These results clearly support the concept of extended plasma profiles of omeprazole being beneficial in optimising control of acid secretion.

Claims

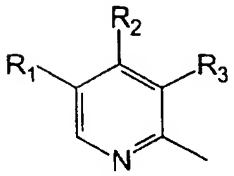
1. An administration regimen giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor, characterized in that the H^+, K^+-ATPase inhibitor is a compound with the formula I



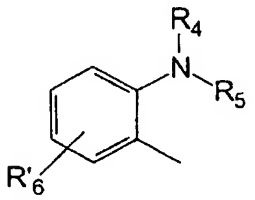
I

wherein

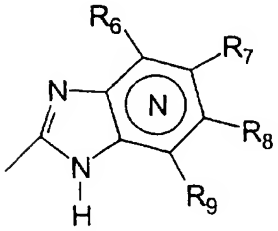
Het_1 is



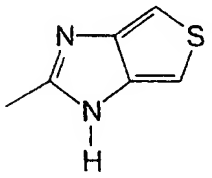
or



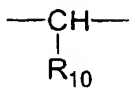
Het_2 is



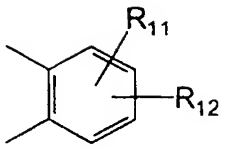
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

2. An admimistration regimen according to claim 1 characterized in that the H^+, K^+-ATPase inhibitor is a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

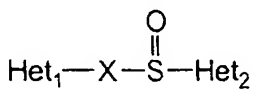
3. An administration regimen giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to any of claims1 and 2 characterized in that the extended plasma profile is obtained by two or more consecutive oral administrations of a unit dose of the H^+, K^+-ATPase inhibitor with 0.5 - 4 hours intervals.

4. An administration regimen giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to claim 1 characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical preparation which releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

5. An administration regimen according to claim 1, characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical preparation which releases the H^+, K^+-ATPase inhibitor for absorption with an almost constant rate during an extended time period.

6. An administration regimen according to any of claims 1 - 5 characterized in that the extended plasma profile is received during 2 - 12 hours.

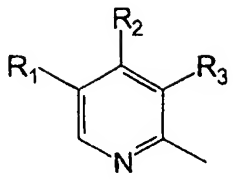
7. An oral pharmaceutical composition giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor, characterized in that the H^+, K^+-ATPase inhibitor is a compound with the formula I



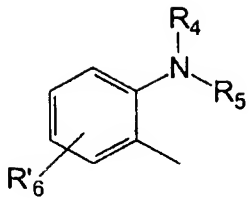
I

wherein

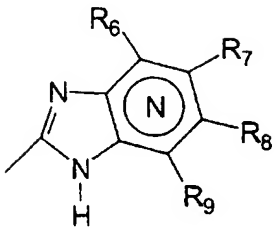
Het_1 is



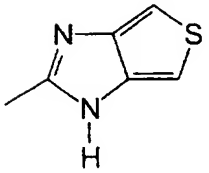
or



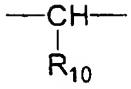
Het_2 is



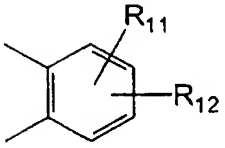
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

8. An oral pharmaceutical preparation according to claim 7, characterized in that the H^+, K^+-ATPase inhibitor is acompound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

9. An oral pharmaceutical preparation giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to claim 7 characterized in that the pharmaceutical preparation releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

10. An oral pharmaceutical preparation according to claim 7, characterized in that the pharmaceutical preparation releases the H^+, K^+-ATPase inhibitor for absorption with an almost constant rate during an extended time period.

11. An oral pharmaceutical preparation giving an extended blood plasma profile of a H^+, K^+-ATPase inhibitor according to any of claims 7 - 10 characterized in that the extended plasma profile is received during 2 -12 hours.

12. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

13. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

14. Use of H^+, K^+ - ATPase inhibitor with the formula I defined in claim 1, for the preparation of a pharmaceutical composition with extended release.

15. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any of claims 7 - 10.

16. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any claims 7 - 10.

17. A method for receiving an extended plasma profile of a H^+, K^+- ATPase inhibitor by administering to a patient in need thereof a pharmaceutical preparation with extended release of a H^+, K^+- ATPase inhibitor as defined in claim 1.

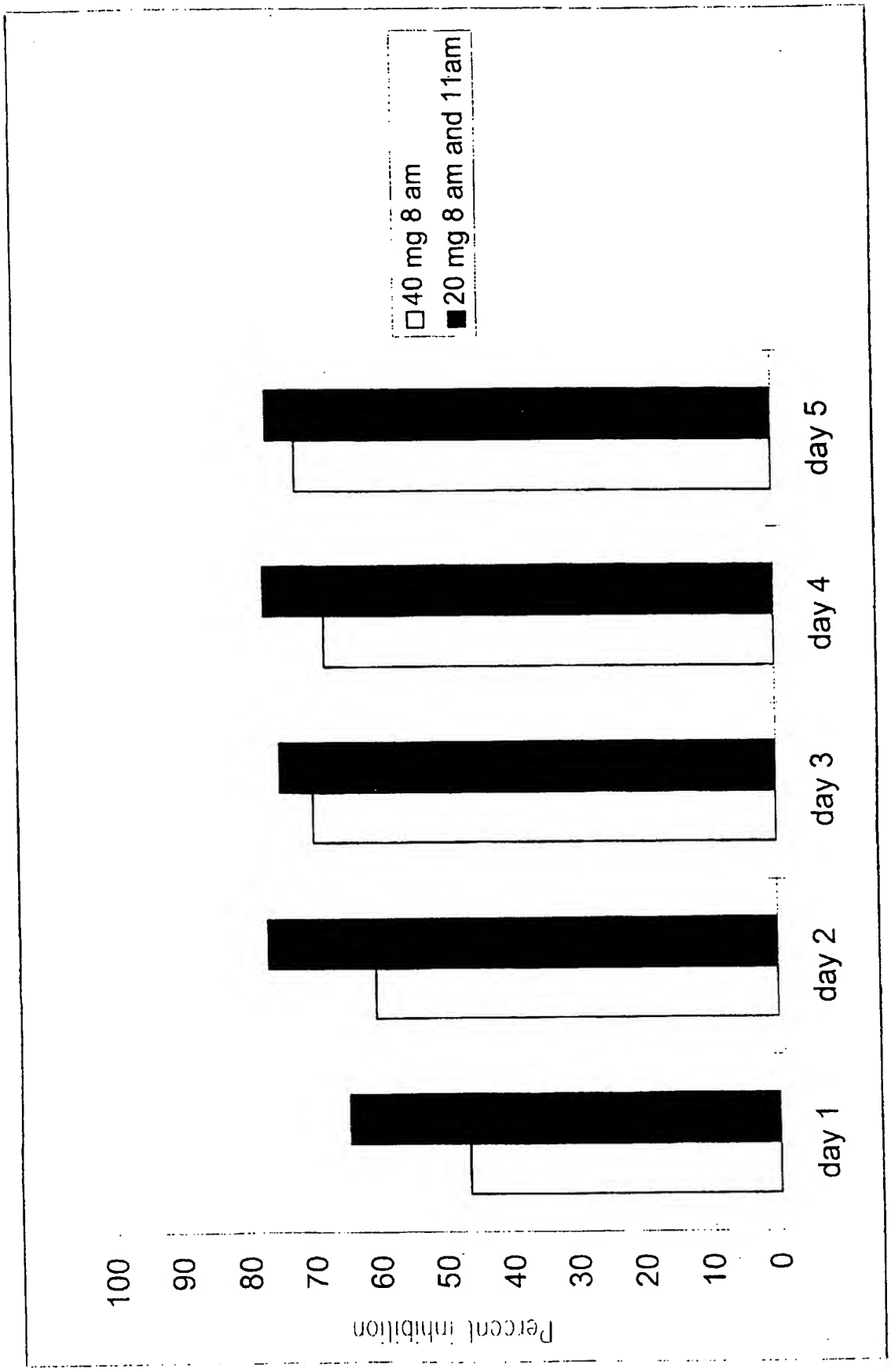

40 mg 8 am
20 mg 8 am and 11am
Percent inhibition
0
10
20
30
40
50
60
70
80
90
100
day 1
day 2
day 3
day 4
day 5

Figure 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01098

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/00, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96), page 15, line 16 - line 22	1-17
X	US 4853230 A (KURT I. LOVGREN ET AL), 1 August 1989 (01.08.89), column 10, line 51 - line 62	1-17
A	John E. Hoover "Remington's Pharmaceutical Sciences", 1975, Mack Publishing Company, Pennsylvania, page 702, column 1, line 43 - column 2, line 6	1-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 1997	22 -10- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01098

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 15-17 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds and the compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/97

International application No.
PCT/SE 97/01098

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601623 A1	25/01/96	AU 2993795 A	09/02/96
		CA 2170647 A	25/01/96
		CN 1134666 A	30/10/96
		CZ 9600732 A	17/07/96
		DE 723436 T	11/09/97
		EP 0723436 A	31/07/96
		ES 2100142 T	16/06/97
		FI 961057 A	29/03/96
		HR 950349 A	30/06/97
		HU 75775 A	28/05/97
		HU 9600573 D	00/00/00
		IL 114450 D	00/00/00
		JP 9502739 T	18/03/97
		NO 960950 A	07/03/96
		NZ 289948 A	27/07/97
		PL 313387 A	24/06/96
		SE 9402433 D	00/00/00
		ZA 9505548 A	08/01/96
		SE 9402432 D	00/00/00
US 4853230 A	01/08/89	AT 139692 T	15/07/96
		AU 603568 B	22/11/90
		AU 7192287 A	05/11/87
		CA 1302891 A	09/06/92
		CN 1025151 B	29/06/94
		CS 268535 B	14/03/90
		CS 8703073 A	13/06/89
		DE 3751851 D,T	31/10/96
		DE 3783386 A	18/02/93
		DK 169987 B	24/04/95
		DK 215987 A	31/10/87
		EG 18517 A	30/04/93
		EP 0244380 A,B	04/11/87
		SE 0244380 T3	
		EP 0502556 A,B	09/09/92
		SE 0502556 T3	
		EP 0565210 A	13/10/93
		ES 2010648 T	16/07/94
		ES 2089277 T	01/10/96
		FI 91708 B,C	29/04/94
		GB 2189699 A	04/11/87
		HK 55497 A	09/05/97
		HK 104095 A	07/07/95
		HR 920855 A	30/06/95
		IE 61837 B	30/11/94
		JP 1946242 C	10/07/95
		JP 6067837 B	31/08/94
		JP 62258316 A	10/11/87
		KR 9504886 B	15/05/95
		LT 2260 A	15/12/93
		NO 174952 B,C	02/05/94
		SI 8710680 A	31/12/96
		SU 1709894 A	30/01/92